

Current Review

In Clinical Science



Neurostimulation—Past, Present, and Beyond

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Neurostimulation as a treatment for epilepsy has been around for almost 20 years in the form of vagus nerve stimulation. Newer types of neurostimulation are being developed and stand on the brink of approval for use. The two newest therapies, not yet approved in the United States, are deep brain stimulation and the Responsive Neurostimulator System. In fact, in Europe, approval has already been given for deep brain stimulation and newer forms of vagus nerve stimulation. Efficacy is similar between these therapies, and side effects are moderate, so what will be the future? The challenge will be to learn how to use these therapies correctly and offer the right treatment for the right patient.

Despite the development of new antiepileptic drugs (AEDs), of which there are now 24 in total available in the United States, there are still many patients suffering from continued seizures. Patients with refractory epilepsy should initially be evaluated for resective epilepsy surgery. Neurostimulation is not a replacement for resective surgical options. Unfortunately, not all patients can be cured of their seizures by epilepsy surgery, therefore other methodologies have to be developed as well. Of the nonpharmacologic therapies available, vagus nerve stimulation (VNS) has been the procedure that has been the most accessible and best studied. The therapy has been approved since 1997 in the United States, and in Europe since 1994. Efficacy can be compared with that of a newer AED (1). Deep brain stimulation (DBS) has been studied in different forms, but only a double-blind study of bilateral stimulation of the anterior nucleus of the thalamus (2) has been accepted by the European Medicinal Agency as showing efficacy and is now approved as a therapy for epilepsy in Europe. DBS for epilepsy has not been approved in the United States. The closed-loop system (the Responsive Neurostimulator System, RNS) is also under development, and a double-blind study has also been completed (3), but approval for use in refractory focal onset epilepsy patients is pending.

Anatomy and Mechanisms of Action

VNS therapy is designed to stimulate the peripheral vagus nerve, most often the left vagus nerve, which is composed of 80% afferent fibers (4). The stimulus has been shown by animal experiments to converge on the nucleus of the tractus solitarius, which then converges on the locus coeruleus (4).

Inhibition of noradrenalin release from the Locus Coeruleus inhibits the antiseizure response in animals (5). PET and fMRI studies (6) have shown that peripheral stimulation of the vagus nerve causes increases in brain metabolism in different areas of the brain, mainly thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, and medulla. Among several hypotheses, VNS could simply be a peripheral variation of thalamic stimulation. This idea is intriguing, and it is notable that efficacy results are similar in the pivotal studies of these two modalities (1–3, 7). Many ideas have emerged through the years concerning the mechanism of action of VNS neurostimulation. Animal experiments and research in humans treated with VNS have included electrophysiological studies (EEG, EMG, Evoked Potentials), as well as functional anatomic brain imaging studies (PET, SPECT, fMRI, c-fos, densitometry) (8, 9). Also, from the extensive clinical experience with VNS, interesting clues concerning the mechanism of action have arisen, but nothing is conclusive. One hypothesis is that peripheral VNS may have a network-modifying influence in the brain, changing synaptic connections. The more chronic effects of VNS are thought to be a reflection of modulatory changes in subcortical site-specific synapses with the potential to influence larger cortical areas. To date, however, the precise mechanism of action of VNS, and how it reduces seizures, is still elusive even though it has been in use and has been the subject of experimental research for many years.

The rationale for DBS of the thalamus is that the thalamus can serve as a relay station through thalamocortical networks, thereby inhibiting or disrupting rhythmic depolarization signals from spreading and causing overt seizures. The anterior nucleus of the thalamus (ANT) is implicated in seizure spread, and stimulation of the ANT has been shown to reduce synchrony and increase inhibition in hippocampus or neocortex (10). In animal studies, low-frequency stimulation of ANT leads to the generation of recruiting rhythms and synchronizes the

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pattern of EEG activity, making the cortex more susceptible to seizures, whereas high-frequency stimulation leads to EEG desynchronization, which hopefully should produce an anti-seizure effect (11).

The RNS system is designed to work through seizure detection. This is an individualized treatment, whereby a detecting electrode is placed near the seizure focus as well as a stimulating electrode. In other words, the seizure focus or foci must always be known and identified before implantation of the device. The system then provides real-time electrographic analysis and automatic delivery of a responsive stimulation to a signal that is detected as being epileptiform. The idea is that an evolving seizure will be aborted by stopping its development and propagation (12).

It should be noted that the exact mechanism of action of a number of the AEDs is also not fully understood, and new details are continually forthcoming, even concerning the oldest antiepileptic drugs.

Implantation

When implanted, the VNS generator is placed in the upper left chest with the stimulating lead attached to the left vagus nerve in the neck. The generator is then programmed externally with a programming wand attached to a personal computer. Frequency, output current, pulse width, signal-on time, signal-off time, and magnet parameters (discussed below) are adjusted by the physician using the programming system.

Besides the intermittent stimulation programmed in the device by the physician, there is also a magnet provided that can restart the programming at its own parameters for a brief time in order to try to abort an emerging seizure. Magnet parameters may be programmed to their own settings by the same method as for the continual intermittent stimulation parameter settings. When a patient experiences an aura or a simple partial seizure, they can use the magnet to abort the pending seizure. In a number of studies, the magnet function seems to be useful in about 30 to 40 percent of patients (13, 14). Using the magnet helps patients develop a means to exert control over their seizures and not just stand by as an observer waiting for them to develop. Perhaps, after a while, the magnet response might even become a positive conditioned behavior. Average chronic stimulation parameters are as follows: between 1.5 and 2.25 mA, 20 to 30 Hz, 250 to 500 microseconds, on 30 seconds, off 3 to 5 minutes, and sometimes fast cycling with 7 seconds on and 14 seconds off. Battery life is dependent on the type of stimulation given.

DBS electrodes are implanted bilaterally in the anterior nuclei of the thalamus. The stimulator and battery are implanted under the left clavicle, where it is accessible for adjusting the parameters used. High-frequency stimulation is used at around 5 V, 145 pulses per second (pps), 90 microseconds, and with a cycle time of 1 minute on and 5 minutes off (2).

For RNS, a stimulating electrode and a detection electrode are placed near the seizure focus, and the stimulation device with battery is placed in a recess in the skull bone. Programming of the device is performed using a wand attached to a computer as in VNS and DBS. Responsive stimulation requires

systems that detect abnormal electrographic activity and provide stimulation (closed loop). It aims to suppress epileptiform activity by delivering stimulation directly in response to electrographic epileptiform activity. The implantable components of the system include a cranially implanted neurostimulator, and either intracranial depth or strip leads. It can stimulate two different epileptogenic zones separately (12). A wide range of stimulating parameters can be used, with ranges in stimulating widths from 40 to 1000 microseconds, at 1 to 333 Hz, and from 0.5 to 12 mA.

Efficacy

Compared with the new AEDs, VNS has similar efficacy results in clinical trials (1, 7), but the long-term efficacy results are more positive. Retention after 3 to 5 years is better than for AEDs, but this is also because it is harder to remove a VNS than to discontinue a drug (7, 15). Unlike drugs, where efficacy may decline with time, efficacy with VNS continues to improve over a period of 18 months to 2 years. There have been no new emergent side effects or tolerance development over observation times of up to 8 to 12 years (16). VNS battery life is now 8 to 10 years depending on the stimulation parameters used. Patients whose battery life has ended often experience a deterioration with increased seizure frequency. Until recently, with the development of generators with advanced technology, the only sign that the device had stopped functioning was when the patient experienced an increase in seizure frequency or seizure severity or no longer felt the stimulation. In these situations, each patient actually served as his own control, demonstrating that the reduction in seizure frequency observed when using VNS was not a function of the regression towards the mean or an effect of a seasonal fluctuation of seizure frequency. From the clinical trials and registry studies, it is known that over 70% have elected to replace VNS, indicating that VNS can be considered to be effective and not just an expensive placebo (15). The VNS now has a battery indicator, so the device can be replaced before end of service, thereby eliminating the guessing game of when to replace the battery. If in doubt about the efficacy of the VNS, there is still the option to allow the generator to stop and see if seizure-control deteriorates. Nevertheless, VNS is not a replacement for resective surgery, as the efficacy of the VNS is more comparable to that of an AED than surgical treatment (1, 7, 9).

VNS has been studied in most seizure types and syndromes. Although mainly case reports, there have been studies in Lennox–Gastaut syndrome (17) showing efficacy. A large patient registry tracked patients for years, which also indicated that VNS has a broad spectrum of activity equal to that of some AEDs (which have also not been evaluated in adequately powered double-blind placebo-controlled clinical trials for primary generalized epilepsies).

Efficacy for DBS as described in the SANTE (stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy) study showed similar results to that of VNS. At the end of the double-blind, 3-month period, controls experienced a 14.9% median reduction of seizures, while the active group had a 40.5% median reduction of seizures. In the long-term maintenance, seizures continued to become less, and



by the end of 2 years, the median seizure reduction was 56%. Fourteen patients were seizure-free for 6 months (2).

The results for RNS are remarkably similar. At the end of the double-blind, 3-month period, controls experienced 17.3% reduction of seizures, while in the active group, there was a 37.9% reduction of seizures. In the long-term maintenance, seizure frequency continued to fall, and by the end of 2 years, the median seizure reduction was 56% (3).

Anterior nucleus of the thalamus stimulation (in this context, DBS) has not been systematically studied in patients, other than those with focal onset seizures, as has RNS. Other nonrandomized studies of DBS of other brain regions have indicated, however, that it might also be a broad-spectrum treatment modality. Controlled studies, however, need to be done to make this determination.

Adverse Effects

Neurostimulation procedures are operative. So far all the devices need to be implanted, which entails an operation and recovery. There are, however, some external VNS devices under development, one that just received approval in Europe. However, the efficacy of this device on seizure reduction has not been extensively evaluated (18).

All operative procedures have risks involved. Interoperative events for VNS are very low and often not serious. Dissection of the vagus nerve during implantation of the electrodes can, however, cause left vocal cord paralysis, which may take a few months to recover. DBS and RNS have higher risks of bleeding and infection as they involve implantation in the brain and not just peripherally.

Because of the spread of the current to the vocal cords and other fibers of the vagus nerve, hoarseness, coughing, tingling, and pain, and dyspnea can occur as common side effects of VNS (7). These often resolve with time but may be rate limiting and prevent maximal stimulation. There is another device now available in Europe that has developed electrode methodology (BioControl, Israel) for reducing the side effects and thus will hopefully facilitate tolerability of higher stimulation parameters (19). This device is currently going through clinical trials for cardiac failure but can also be used and is approved for epilepsy treatment in Europe (20).

Simulation from DBS and RNS is not perceived by the patient; therefore, once implanted, side effects have been very few and none that have been specific to the methodology (2, 3).

Site infections from the SANTE study were 12.7%. More chronic side effects that were significant compared with placebo were depression in 14.8%, memory impairment in 13%, and confusion in 9.3%. By 13 months, there were 18.2% who had reported paresthesias, and 10.9% with implant site pain. Another 16.4% withdrew from the study. In addition, 4.5% had hemorrhages discovered when doing a postoperative MRI but did not have clinical complaints (2).

RNS adverse events reported by year in the pivotal study were implant site infections, 6%; implant site pain, 15%; headache, 20%; implant site swelling, 8%; dysesthesia, 6%; Inc. GTC, 5.8%; Inc. CPS, 4.7%; depression, 3.1%; and memory impairment, 4.2%. In other words, long-term side effects were generally manageable and moderate to minor (3).

Pregnancy and Teratogenicity

VNS does not affect pregnancy or have any teratogenic properties. Therefore, it is safe to use during pregnancy. After 23 years of use, there has still not been a report of VNS causing adverse reactions during pregnancy or on the fetus (21, 22).

There are no reports on pregnancies with DBS and RNS, but rationally it does seem unlikely that this will be a problem. Patients with other conditions using DBS at other sites in the brain have reported successfully completed pregnancies (23).

MRI Compatibility

VNS devices are now approved for use during MRI investigations using head coils and 1.5- to 3-tesla machines. It is recommended that the device be turned off during the procedure. DBS is MRI compatible.

The Future

Even at the time of the review, other means of neuromodulation were being tested, including transcranial magnetic stimulation (TMS), trigeminal stimulation, occipital stimulation, and hippocampal stimulation. The most important rule is that comparative double-blind and preferably (when possible) placebo- or sham-controlled trials should be carried out. The studies should be longer than the usual drug trial, as 3 months observation time is not enough. Time and again for all types of neurostimulation for epilepsy, the long-term follow-up results are better than the short-term, 3-month evaluation periods.

Remarkably, the results of the clinical trials for RNS and DBS are very similar to those of VNS, although it could be that each of these stimulation-modulating therapies is effective in different populations. Also, it may be that the optimal stimulating parameters are not yet known. There have been no comparative trials, therefore there is no means of deciding which of the modalities is preferable or more effective if at all.

On the horizon, new VNS devices with refined electrodes with the promise of fewer side effects during stimulation will be available, and as has been mentioned before, one such device is already approved in Europe. In addition, an external VNS device has also just been approved in Europe but not in the United States.

Because there is a lack of adequate treatments for refractory epilepsy patients, the general search for less-invasive treatments in medicine and the progress in biotechnology have led to a renewed and increasing interest in neurostimulation as a therapeutic option, and that is what we are currently witnessing.

Major issues remain unresolved. The ideal targets and stimulation parameters for VNS, DBS, RNS, TMS, and trigeminal stimulation (TGS) are unknown. The types of patients, seizures, or epilepsy syndromes, which are most sensitive to specific types of neurostimulation are unknown. The elucidation of the mechanism of action of different neurostimulation techniques requires more basic research in order to demonstrate the potential of this modality. One thing is for sure: this area of research and treatment is exploding and the future is exciting.

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